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Chapter 60: Lung Cancer

INTRODUCTION

- *Lung cancer* is a solid tumor originating from the bronchial epithelial cells that have acquired multiple genetic lesions and express a variety of phenotypes. This chapter distinguishes between nonsmall cell lung cancer (NSCLC; adenocarcinoma [~50%], squamous cell carcinoma [<30%], and large cell carcinoma) and small cell lung cancer (SCLC; ~15% of all lung tumors) because they have different natural histories and responses to therapy.
- Mutations cause activation of proto-oncogenes, inhibition of tumor suppressor genes, and production of autocrine (self-stimulatory) growth factors, contributing to cellular proliferation and malignant transformation in lung tissue. Many molecular alterations are common to both SCLC and NSCLC, but certain mutations are found more frequently in specific subtypes of lung cancer and can be potentially treated with targeted interventions.

CLINICAL PRESENTATION

- The most common initial signs and symptoms are cough, dyspnea, chest pain, or discomfort, with or without hemoptysis. Many patients also exhibit systemic symptoms such as anorexia, weight loss, and fatigue.
- Disseminated disease can cause neurologic deficits from central nervous system (CNS) metastases, bone pain or pathologic fractures secondary to bone metastases, or liver dysfunction from hepatic involvement.
- Paraneoplastic syndromes are signs and symptoms that occur at sites away from the tumor location(s) and are not associated with direct tumor involvement. They occur more frequently with lung cancer than any other tumor and more frequently with SCLC than with NSCLC.

DIAGNOSIS

- Computed tomography (CT) scans of the chest and upper abdomen are common initial radiologic evaluations. The staging workup can include an endobronchial ultrasound, positron emission tomography (PET) scan, or other tests. Integrated CT–PET technology appears to improve diagnostic accuracy in staging NSCLC over CT or PET alone.
- Pathologic confirmation is established by examination of sputum cytology and/or tumor biopsy. The tissue sample not only confirms malignancy but also is necessary to determine the specific tumor type and to provide tissue for molecular analysis.
- All patients must have a thorough history and physical examination to detect signs and symptoms of the primary tumor, regional spread, distant metastases, paraneoplastic syndromes, and ability to tolerate aggressive therapy.

STAGING

- Clinical staging of NSCLC with the TNM system incorporates tumor size (T), extent of nodal involvement (N), and presence or absence of distant metastases (M).
- A simpler system is commonly used to compare therapeutic modalities. Stage I includes tumors confined to the lung without lymphatic spread, stage II includes large tumors with ipsilateral peribronchial or hilar lymph node involvement, stage III includes other lymph nodes and regional involvement, and stage IV includes any tumor with distant metastases.

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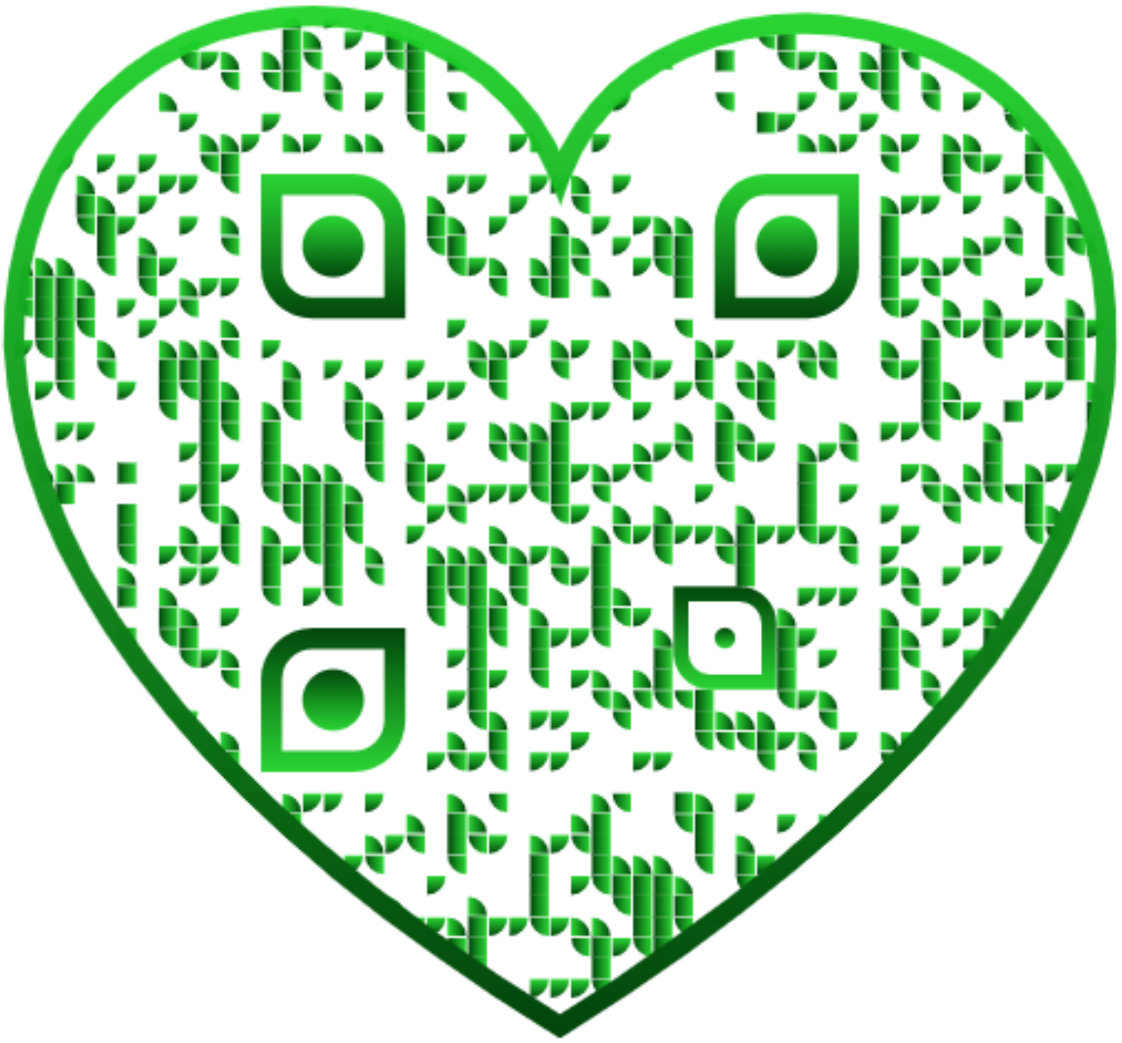

- The TNM staging system can also be used for SCLC; however, a two-stage classification is more commonly used. Limited disease is confined to one hemithorax and can be encompassed by a single radiation port. All other disease is classified as extensive.

TREATMENT

NONSMALL CELL LUNG CANCER

- Goals of Treatment: Definitive cure is the desired outcome with early-stage disease. Prolongation of survival is desired in patients with advanced-stage disease. All therapies should improve quality of life.
- Surgery, radiation, and systemic therapies with cytotoxic chemotherapy, immunotherapy, or targeted therapies are used in the management of NSCLC. Treatment modalities are determined by stage- and patient-specific factors.
- Local disease (stages IA and IB) is associated with a favorable prognosis. Surgery is the primary treatment and may be used alone or in combination with radiation therapy (RT) and/or systemic therapy.
- Stage IIA and IIB diseases are treated with surgery, followed by four cycles of adjuvant chemotherapy (**Table 60-1**). The optimal regimen is not clear. Screen patients with operable NSCLC for targetable genetic mutations to identify treatment options. Chemoradiotherapy is recommended for medically inoperable patients if tolerated; concurrent administration of chemotherapy and RT is preferred.
- Adjuvant targeted therapy improved:

  ✓ Overall survival (OS) compared to placebo in epidermal growth factor receptor (EGFR)–positive disease (stage IB to IIIA) with 3 years of **osimertinib** with or without chemotherapy.

  ✓ Disease-free survival (DFS) compared to platinum-based chemotherapy in anaplastic lymphoma kinase (ALK)–positive disease with **alectinib**.

  ✓ DFS at 3 years after 1 year of **atezolizumab** in patients with stage II–IIIA disease positive for programmed death-ligand 1 (PD-L1).

  ✓ Median DFS compared to placebo after 1 year of **pembrolizumab** in patients with stage IB–IIIA disease regardless of PD-L1 expression.

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TABLE 60-1

Common Chemotherapy Regimens Used in the Adjuvant Treatment of Nonsmall Cell Lung Cancer

Regimen	Drugs and Doses	Frequency and Number of Cycles
Cisplatin/Etoposide	Cisplatin 100 mg/m^2 IV day 1 Etoposide 100 mg/m^2 IV daily on days 1, 2, and 3	Every 28 days for 4 cycles
Cisplatin/Vinorelbine	Cisplatin 50 mg/m^2 IV days 1 and 8 Vinorelbine 25 mg/m^2 IV days 1, 8, 15, and 22	Every 28 days for 4 cycles
	Cisplatin 100 mg/m^2 IV day 1 Vinorelbine 30 mg/m^2 IV days 1, 8, 15, and 22	Every 28 days for 4 cycles
Carboplatin/Paclitaxel	Carboplatin AUC 6 IV day 1 Paclitaxel 200 mg/m^2 IV day 1	Every 21 days for 4 cycles
Cisplatin/Pemetrexed	Cisplatin 75 mg/m^2 IV day 1 Pemetrexed 500 mg/m^2 IV day 1	Every 21 days for 4 cycles (for nonsquamous histology only)

AUC, area under the curve; IV, intravenous.

LOCALLY ADVANCED DISEASE (STAGE III)

- Optimal outcomes for stage III disease are achieved with multimodality therapy. Patients with operable disease should be considered for surgery preceded or followed by systemic chemotherapy. Current recommendations for patients with resectable stage IIIA disease include chemotherapy (**Table 60-1**), followed by surgery or radiation, depending on individual patient and tumor features. Neoadjuvant chemotherapy with a tumor size greater than 4 cm or having positive lymph node involvement should include **nivolumab.**
- Patients with stage IIIA disease who are not surgical candidates or have a tumor that cannot be resected are typically treated with both a platinum-containing regimen and concurrent RT. Stage IIIB and IIIC NSCLC are considered unresectable. Administer induction therapy with chemoradiation followed by consolidation therapy in those who respond with the PD-L1 inhibitor, **durvalumab,** for 1 year to improve progression-free survival (PFS) and OS.

ADVANCED (STAGE IV) AND RELAPSED DISEASE

- Patients with stage III disease who are not candidates for radiation are treated like those with stage IV disease. Chemotherapy is administered to palliate symptoms, improve quality of life, and increase survival. Therapy depends on patient-specific factors (performance status is most important) and tumor characteristics.
- Three pathways have been identified for advanced NSCLC: (1) immune sensitive (PD-L1+), (2) targetable genetic mutation-driven, which is further divided based on the sensitizing mutation, and (3) non–biomarker-driven therapy treatment, which is further classified as squamous histology or nonsquamous histology due to drug toxicity and efficacy. Select regimens for first-line treatment of advanced NSCLC are outlined in **Table 60-2**; second-line treatment options are found in **Table 60-3**.
- Patients with advanced lung cancer positive for targetable genetic driver mutations have treatment options based on the specific mutation: ALK, BRAF^{V600E}, EGFR, ERBB2 (HER2), KRAS, MET, NTRK, RET-fusion, or ROS1.

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- Treatment options for patients with advanced lung cancer and a targetable genetic driver mutation include the following (see **Table 60-4**) (consult practice guidelines for the most up-to-date recommendations):

  ✓ Treat patients with a tumor that harbors a *mutation in the EGFR receptor* with a first-line EGFR kinase inhibitor. First- and second-generation EGFR kinase inhibitors include **afatinib**, **erlotinib,** or **gefitinib.** A meta-analysis suggests that these three agents have similar PFS results and response rates about two times higher than chemotherapy. **Dacomitinib** is another second-generation irreversible inhibitor. **Osimertinib**, a third-generation EGFR kinase inhibitor, shows the most impressive activity in EGFR-positive tumors and is considered first-line therapy. In addition to significantly longer PFS, osimertinib has improved CNS penetration, resulting in improved CNS response rates and less CNS disease as the cause of progression. **Amivantamab** plus **lazertinib** has shown improved PFS and duration of response compared to osimertinib as first-line therapy. However, this combination is associated with increased adverse drug reactions, which resulted in higher rates of discontinuation (10%) compared to osimertinib (3%). Subsequent therapy after progression during treatment with an EGFR inhibitor depends on initial treatment and further genetic evaluation. Most patients will proceed to a platinum doublet chemotherapy with or without an immunotherapy agent.

  ✓ First-generation ALK inhibitors **crizotinib** and **ceritinib** established ALK inhibition as superior to chemotherapy. Patients with a tumor with an *ALK rearrangement* should receive initial treatment with a second-generation (**alectinib** or **brigatinib)** or third-generation (**lorlatinib)** ALK inhibitor. Patients who relapse while receiving initial ALK-targeted therapy can receive an agent from the next generation.

  ✓ Patients with a tumor with the *BRAF V600E mutation* should receive combination therapy with two kinase inhibitors, **trametinib** and **dabrafenib**.

  ✓ *ERBB2 (HER2) overexpression or mutations* occur in about 3% of patients with NSCLC. Antibody drug conjugates that combine chemotherapy with a HER2-directed antibody, like **fam-trastuzumab deruxtecan** and **ado-trastuzumab**, are recommended in those who have progressed with prior systemic therapy. **Trastuzumab-emtansine** is also an option.

  ✓ *KRAS mutations* are associated with cigarette smoking and carry a poor prognosis. First-line platinum-based chemotherapy ± immune checkpoint inhibitor (ICI) (eg, **sotorasib, adagrasib)** is recommended for these patients.

  ✓ *MET mutations* can be treated with **capmatinib** or **tepotinib**.

  ✓ **Larotrectinib** is used to treat tumors positive for *neurotrophic receptor kinases (NTRK) gene fusion.* **Entrectinib** and **repotrectinib** are also options with *NTRK* gene fusions.

  ✓ In patients with *RET gene rearrangements*, selective RET inhibitors, **selpercatinib,** and **pralsetinib** can be used in patients who have progressed on chemotherapy and those who are treatment naïve.

  ✓ Ceritinib, crizotinib, and entrectinib are first-line agents for tumors with a *mutation in ROS1*; lorlatinib, entrectinib, and repotrectinib are potential second-line therapies.

- Patients with PD-L1+ tumors and no sensitizing mutations are eligible for first-line immunotherapies with ICIs, including atezolizumab, **cemiplimab,** durvalumab, nivolumab, and pembrolizumab. These agents may be used alone or in combination with chemotherapy or a CTLA-4 inhibitor, **ipilimumab** and **tremelimumab**. The percentage of PD-L1 expression on tumor cells is measured by tumor proportion score (TPS); this drives selection of treatment. Patients are divided into three distinct categories: PD-L1 TPS ≥50%, PD-L1 TPS 1%–49%, and PD-L1 TPS <1% (see **Table 60-2**).

- Combination chemotherapy is the standard of care for managing NSCLC without targetable genetic mutations. Platinum-based chemotherapy doublets are preferred. Guidelines recommend adding bevacizumab, a recombinant, humanized monoclonal antibody that neutralizes vascular endothelial growth factor to chemotherapy with advanced NSCLC of nonsquamous cell histology, no recent hemoptysis, no CNS metastasis, and not receiving therapeutic anticoagulation.

- Monotherapy with nivolumab, pembrolizumab, atezolizumab, **docetaxel,** or pemetrexed is considered for second-line therapy in patients with a good performance status who progress during or after first-line chemotherapy. Nivolumab, pembrolizumab, and atezolizumab are options in the second-line setting for patients who are immunotherapy-naive.

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- For patients who have failed initial treatment with immunotherapy, second-line treatment with docetaxel, docetaxel-**ramucirumab**, or pemetrexed (if pemetrexed was not used as maintenance therapy) is recommended (see **Table 60-3**).

TABLE 60-2

Selected Regimens for the First-Line Treatment of Advanced-Stage NSCLC

	Adenocarcinoma, Large Cell, NSCLC NOS		Squamous Cell Carcinoma	
Place in Therapy	**PD-L1 ≥50%**	**PD-L1 1%–49%**	**PD-L1 ≥50%**	**PD-L1 1%–49%**
First line	Pembrolizumab 200 mg IV on day 1 every 21 days or 400 mg IV on day 1 every 42 days Repeat until disease progression or unacceptable toxicity for a maximum of 2 years	Platinum + pemetrexed + pembrolizumab Cisplatin 75 mg/m^2 or carboplatin AUC 5 IV on day 1 Pemetrexed 500 mg/m^2 IV on day 1 Pembrolizumab 200 mg IV on day 1 Repeat cycle every 3 weeks × 4 cycles—pembrolizumab maintenance up to 31 additional doses or until progression	Pembrolizumab 200 mg IV on day 1 every 21 days or 400 mg IV on day 1 every 42 days Repeat until disease progression or unacceptable toxicity for a maximum of 2 years	Carboplatin + paclitaxel + pembrolizumab Carboplatin AUC 6 IV on day 1 Paclitaxel 200 mg/m^2 IV on day 1 or nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 Pembrolizumab 200 mg IV on day 1 Repeat cycle every 3 weeks × 4 cycles–Pembrolizumab maintenance up to 31 additional doses or until progression
	Atezolizumab 840 mg IV on day 1 repeat every 14 days or 1200 mg IV on day 1 repeat every 21 days or 1680 mg IV on day 1 repeat every 28 days Continue until disease progression or unacceptable toxicity	Platinum + pemetrexed + cemiplimab Cisplatin 75 mg/m^2 or carboplatin AUC 5 IV on day 1 Pemetrexed 500 mg/m^2 IV on day 1 Cemiplimab 350 mg IV on day 1 Repeat cycle every 3 weeks × 4 cycles—cemiplimab maintenance up to 31 additional doses or until progression	Carboplatin + paclitaxel + pembrolizumab Carboplatin AUC 6 IV on day 1 Paclitaxel 200 mg/m^2 IV on day 1 or nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 Pembrolizumab 200 mg IV on day 1 Repeat cycle every 3 weeks × 4 cycles Pembrolizumab maintenance up to 31 additional doses or until	Cemiplimab + paclitaxel + platinum Cemiplimab 350 mg IV on day 1 Paclitaxel 200 mg/m^2 IV on day 1 Carboplatin AUC 5–6 IV or cisplatin 75 mg/m^2 on day 1 Repeat every 21 days × 4 cycles Cemiplimab maintenance until disease progression

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			progression	
	Cemiplimab 350 mg IV on day 1 Repeat every 21 days until disease Continue until disease progression or unacceptable toxicity	Atezolizumab + carboplatin + paclitaxel + bevacizumab Atezolizumab 1200 mg IV on day 1 Carboplatin AUC 6 IV on day 1 Paclitaxel 200 mg/m^2 IV on day 1 Bevacizumab 15 mg/kg IV on day 1 Repeat cycle every 3 weeks × 6 cycles Atezolizumab and bevacizumab maintenance until progression	Atezolizumab 840 mg IV on day 1, repeat every 14 days or 1200 mg IV on day 1 repeat every 21 days or 1680 mg IV on day 1 repeat every 28 days Continue until disease progression or unacceptable toxicity	Nivolumab + ipilimumab + carboplatin + paclitaxel Nivolumab 360 mg IV on days 1 and 22 Ipilimumab 1 mg/kg IV on day 1 Paclitaxel 200 mg/m^2 on days 1 and 22 Carboplatin AUC 6 IV on days 1 and 22 Followed by nivolumab and ipilimumab maintenance every 42 days until disease progression or unacceptable toxicity for a maximum of 2 years
	Cemiplimab + paclitaxel + carboplatin Cemiplimab 350 mg IV on day 1 Paclitaxel 200 mg/m^2 IV on day 1 Carboplatin AUC 5–6 IV or cisplatin 75 mg/m^2 IV on day 1 Repeat every 21 days × 4 cycles Cemiplimab maintenance until disease progression	Nivolumab + ipilimumab + carboplatin + pemetrexed Nivolumab 360 mg IV on days 1 and 22 Ipilimumab 1 mg/kg IV on day 1 Pemetrexed 500 mg/m^2 on days 1 and 22 Carboplatin AUC 6 IV or cisplatin 75 mg/m^2 on days 1 and 22 Followed by nivolumab and ipilimumab maintenance every 42 days until disease progression or unacceptable toxicity for a maximum of 2 years	Cemiplimab 350 mg IV on day 1 Repeat every 21 days until disease progression or unacceptable toxicity	Nivolumab + ipilimumab Nivolumab 3 mg/kg IV on days 1, 15, and 29 Ipilimumab 1 mg/kg IV on day 1 Repeat every 42 days until disease progression or unacceptable toxicity for a maximum of 2 years
	Atezolizumab + carboplatin + paclitaxel + bevacizumab Atezolizumab 1200 mg IV on day 1	Nivolumab + ipilimumab Nivolumab 3 mg/kg IV on days 1, 15, and 29 Ipilimumab 1 mg/kg IV on day 1 Repeat every 42 days until disease progression or unacceptable toxicity for a	Cemiplimab + paclitaxel + carboplatin Cemiplimab 350 mg IV on day 1 Paclitaxel 200 mg/m^2 IV on day	Pembrolizumab 200 mg IV on day 1 every 21 days or 400 mg IV on day 1 every 42 days Repeat until disease progression, or unacceptable toxicity for a maximum of 2 years

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	Carboplatin AUC 6 IV on day 1 Paclitaxel 200 mg/m^2 IV on day 1 Bevacizumab 15 mg/kg IV on day 1 Repeat cycle every 3 weeks × 6 cycles Atezolizumab and bevacizumab maintenance until progression	maximum of 2 years	1 Carboplatin AUC 5–6 IV on day 1 Repeat every 21 days × 4 cycles Cemiplimab maintenance until disease progression	
First line: Contraindications to PD-1 or PD-L1 inhibitors	Carboplatin + pemetrexed Carboplatin AUC 5 IV on day 1 Pemetrexed 500 mg/m^2 IV on day 1 Repeat cycle every 3 weeks × 4 or 6 cycles followed by pemetrexed maintenance		Gemcitabine + cisplatin Gemcitabine 1000 mg/m^2 IV on days 1, 8, and 15 Cisplatin 100 mg/m^2 IV on day 1 Repeat cycle every 28 days	

NOS, not otherwise specified; PD-1, programmed cell death protein 1.

TABLE 60-3

Selected Regimens for the Second-Line Treatment of Advanced-Stage NSCLC

Second Line: No previous ICI	Nivolumab
	Atezolizumab
	Pembrolizumab
Second Line: Other recommended	Docetaxel + ramucirumab

TABLE 60-4

Selected Targeted Therapies for Initial Treatment of Advanced, Mutation-Driven NSCLC

Target	Preferred First-Line Regimen	Alternative First-Line Regimens
ALK rearrangement	Alectinib Brigatinib Lorlatinib	Ceritinib Crizotinib

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BRAF V600E	Dabrafenib + trametinib Encorafenib + binimetinib	Vemurafenib Dabrafenib
EGFR exon 19 deletion or exon 21 L858R	Osimertinib High-dose osimertinib (160 mg) by mouth daily (in patients with progressive CNS disease or leptomeningeal disease)	Osimertinib + pemetrexed + cisplatin or carboplatin Amivantamab + lazertinib Erlotinib + bevacizumab Dacomitinib Afatinib Erlotinib Gefitinib
EGFR S768I, L861Q, and/or G179X	Afatinib Osimertinib High-dose osimertinib (160 mg) by mouth daily (in patients with progressive CNS disease or leptomeningeal disease)	Erlotinib 150 mg by mouth daily Gefitinib 250 mg by mouth daily Dacomitinib 45 mg by mouth daily
EGFR exon 20 insertion	Amivantamab + pemetrexed + carboplatin	Systemic therapy for NSCLC
ERBB2 (HER2)	Systemic therapy for NSCLC	Trastuzumab deruxtecan Trastuzumab emtansine
KRAS G12C	Sotorasib	Systemic therapy for NSCLC
MET exon 14 skipping (METex14)	Capmatinib Tepotinib	Crizotinib Systemic therapy for NSCLC
NTRK1/2/3 gene fusion	Larotrectinib Entrectinib Repotrectinib	Systemic therapy for NSCLC
RET rearrangement	Selpercatinib Pralsetinib	Cabozantinib Systemic therapy for NSCLC
ROS1 rearrangement	Entrectinib Crizotinib Repotrectinib	Ceritinib

SMALL CELL LUNG CANCER

- Goals of Treatment: The goals include cure or prolonged survival, which requires aggressive combination chemotherapy. All therapies should improve quality of life.

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Limited Disease

- Use of surgery in SCLC is limited to solitary nodules without evidence of metastasis to lymph nodes.
- SCLC is very radiosensitive; radiation is preferred for treatment of local disease over surgery. Treat limited-stage SCLC with combined chemoradiation, followed by up to 2 years of immunotherapy with durvalumab in patients with a complete response (CR) (see **Table 60-5**).
- Radiotherapy is used to prevent and treat brain metastases, a frequent occurrence with SCLC. Prophylactic cranial irradiation (PCI) is used in patients with limited disease who achieve a CR to reduce the incidence of brain metastases.

TABLE 60-5

Chemotherapy Regimens Used in the Treatment of SCLC

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Regimen	Drugs and Doses
Limited Stage	
Etoposide/cisplatin (EP)	Cisplatin 75 mg/m^2 IV on day 1 Etoposide 100 mg/m^2 IV on days 1–3; repeat cycle every 3 weeks for 4–6 cycles or Cisplatin 60 mg/m^2 IV on day 1 Etoposide 120 mg/m^2 IV on days 1–3; repeat cycle every 3 weeks for 4–6 cycles
Etoposide/carboplatin (EC)	Carboplatin AUC 5–6 IV on day 1 Etoposide 100 mg/m^2 IV on days 1–3; repeat cycle every 3 weeks for 4–6 cycles
Durvalumab consolidation	Durvalumab 1500 mg IV day 1 every 4 weeks for up to 2 years Begin after the completion of chemotherapy
Extensive Stage	
EC + atezolizumab	Carboplatin AUC 5 IV on day 1 Etoposide 100 mg/m^2 IV on days 1–3 Atezolizumab 1200 mg IV on day 1; repeat cycle every 3 weeks for 4 cycles followed by Atezolizumab 1200 mg every 3 weeks or 1680 mg every 4 weeks as maintenance
EP + durvalumab	Carboplatin AUC 5–6 IV on day 1 Etoposide 80–100 mg/m^2 IV on days 1–3 Durvalumab 1500 mg IV on day 1; repeat cycle every 3 weeks for 4 cycles followed by Durvalumab 1500 mg every 4 weeks as maintenance
EC + durvalumab	Cisplatin 75–80 mg/m^2 IV on day 1 Etoposide 80–100 mg/m^2 IV on days 1–3 Durvalumab 1500 mg IV on day 1; repeat cycle every 3 weeks for 4 cycles followed by Durvalumab 1500 mg every 4 weeks as maintenance
Relapsed Disease	
Topotecan	Topotecan 1.5 mg/m^2/day IV days 1–5; repeat every 3 weeks
Lurbinectedin	Lurbinectedin 3.2 mg/m^2/day IV day 1; repeat every 3 weeks
Tarlatamab	Cycle 1: Tarlatamab 1 mg IV day 1, followed by 10 mg IV days 8 and 15 Cycle 2 onwards: Tarlatamab 10 mg IV; repeat every 2 weeks

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Extensive Disease

- The EP regimen is the regimen of choice to treat extensive-stage SCLC. Concurrent administration of the PD-L1 inhibitors atezolizumab or durvalumab to carboplatin/etoposide improves PFS and OS. Discontinue chemotherapy after 4 cycles and continue immunotherapy until disease progression or intolerance of therapy.
- Concurrent radiotherapy is not routinely used in extensive disease. Consider use of PCI when there is response to systemic therapy.

Relapsed Disease

- Relapsed SCLC is usually less sensitive to chemotherapy. **Topotecan** (IV and oral) is considered the second-line treatment of choice, but other agents should be considered because of their modest efficacy. If relapse occurs more than 3 months after first-line chemotherapy, national guidelines recommend single-agent PD-L1 inhibitor (nivolumab or pembrolizumab), gemcitabine, **irinotecan**, paclitaxel, docetaxel, oral etoposide, **temozolomide,** and vinorelbine; CAV regimen (**cyclophosphamide, doxorubicin**, and **vincristine**); and participation in a clinical trial.
- Emerging therapies for relapsed SCLC include single-agent treatments with **lurbinectedin,** an alkylating agent, or **tarlatamab**, a bispecific T-cell engager.
- SCLC that recurs within 3 months of first-line chemotherapy is considered refractory to chemotherapy and unlikely to respond to a second-line regimen. Patients should receive best supportive care or be enrolled in a clinical trial.

EVALUATION OF THERAPEUTIC OUTCOMES

- Evaluate tumor response to chemotherapy for NSCLC at the end of the second or third cycle and at the end of every second cycle thereafter. Patients with stable disease, objective response, or measurable decrease in tumor size should continue treatment until four to six cycles have been administered. Consider maintenance therapy with pemetrexed in responding patients with nonsquamous histology.
- ICIs can display a different response pattern than traditional chemotherapy or targeted therapy. The median time-to-response for ICIs is 10–12 weeks and the initial tumor response can appear radiologically as progression.
- Patients with stages I–III lung cancers (NSCLC and SCLC) who achieved a CR and have no clinical suspicion of recurrent disease should undergo regular surveillance imaging utilizing a diagnostic CT scan of the chest, including the adrenal glands, every 3–6 months for the first 2 years. In addition, a low-dose spiral chest CT scan is recommended annually. Consider brain magnetic resonance imaging (MRI) scan every 3 months for the first year and every 6 months for the second year in patients with SCLC.
- References should be consulted for management of common toxicities associated with the aggressive chemotherapy regimens used for lung cancer.

See Chapter 157, Lung Cancer, authored by Keith A. Hecht and Eve M. Segal, for a more detailed discussion of this topic.

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